Table 2. Amplitudes and latencies of mismatch negativity (MMN) and P300

	Before Concerta treatment		After Concerta treatment			
	Mean	SD	Mean	SD	t value (df = 9)	*P*-value
MMN amplitude (uV)						
Fz	4.2	4.2	9.1	9.1	−1.79	0.107
Cz	3.6	4	6.4	11.5	−0.829	0.429
Pz	2.2	5	8.1	6.4	−2.442	0.037*
C3	3.5	4.8	5.6	6.6	−0.88	0.402
C4	4.5	3.5	9	5.4	−2.718	0.024*
MMN latency (ms)						
Fz	173.1	36.3	188.1	33.2	−1.096	0.302
Cz	185	36.4	193	30.1	−0.558	0.591
Pz	192.8	34.2	192.4	32.3	0.033	0.974
C3	191.4	35.9	191	27.9	0.038	0.97
C4	187.5	31.6	180.9	33.4	0.613	0.555
P300 amplitude (uV)						
Fz	−8.5	16.3	−20.8	16.8	1.643	0.135
Cz	−11.2	11.2	−28.1	17.7	2.785	0.021*
Pz	−17	6.7	−33.3	19.8	2.317	0.046*
C3	−10.7	9.2	−19.2	11.3	2.056	0.07
C4	−11	10.5	−20	12.3	2.192	0.056
P300 latency (ms)						
Fz	376.7	68.1	383.4	54.4	−0.36	0.727
Cz	388.7	67.8	383.4	57.4	0.366	0.723
Pz	357.8	58.2	360.9	68.4	−0.233	0.821
C3	355.1	55.5	373.2	57.5	−0.882	0.401
C4	361.8	53.8	358.7	58.1	0.181	0.861

*$P < 0.05$.

RESULTS

MMN

The grand average MMN from ADHD children after osmotic-release MPH treatment was greater than that before treatment (Fig. 1). The exact figures of amplitudes and latencies are listed in Table 2. The mean MMN amplitudes from ADHD children at Pz and C4 after osmotic-release MPH treatment were significantly greater than those before treatment (Table 2).

P300

The grand average P300 from ADHD children after osmotic-release MPH treatment was greater than that before treatment (Fig. 2). The exact figures of amplitudes and latencies are listed in Table 2. The mean P300 amplitudes from ADHD children at Cz and Pz after osmotic-release MPH treatment were significantly greater than those before treatment (Table 2).

DISCUSSION

In the present study, although there seemed to be visual differences in most electrodes for both MMN and P300 following osmotic-release MPH treatment in ADHD children, significant increases in MMN or P300 amplitudes after osmotic-release MPH treatment were only observed in Pz and C4 or Cz and Pz. These discrepancies may relate to the small sample size and large standard deviation in the present study.

P300 is a potential generated in the final stage of sensory and cognitive processing. The improvement in P300 following osmotic-release MPH treatment in ADHD children is consistent with previous studies.[7–9] As disturbance of the P300 component has been previously suggested as an indicator of impaired cognition,[11,12] these data suggest that cognitive function in

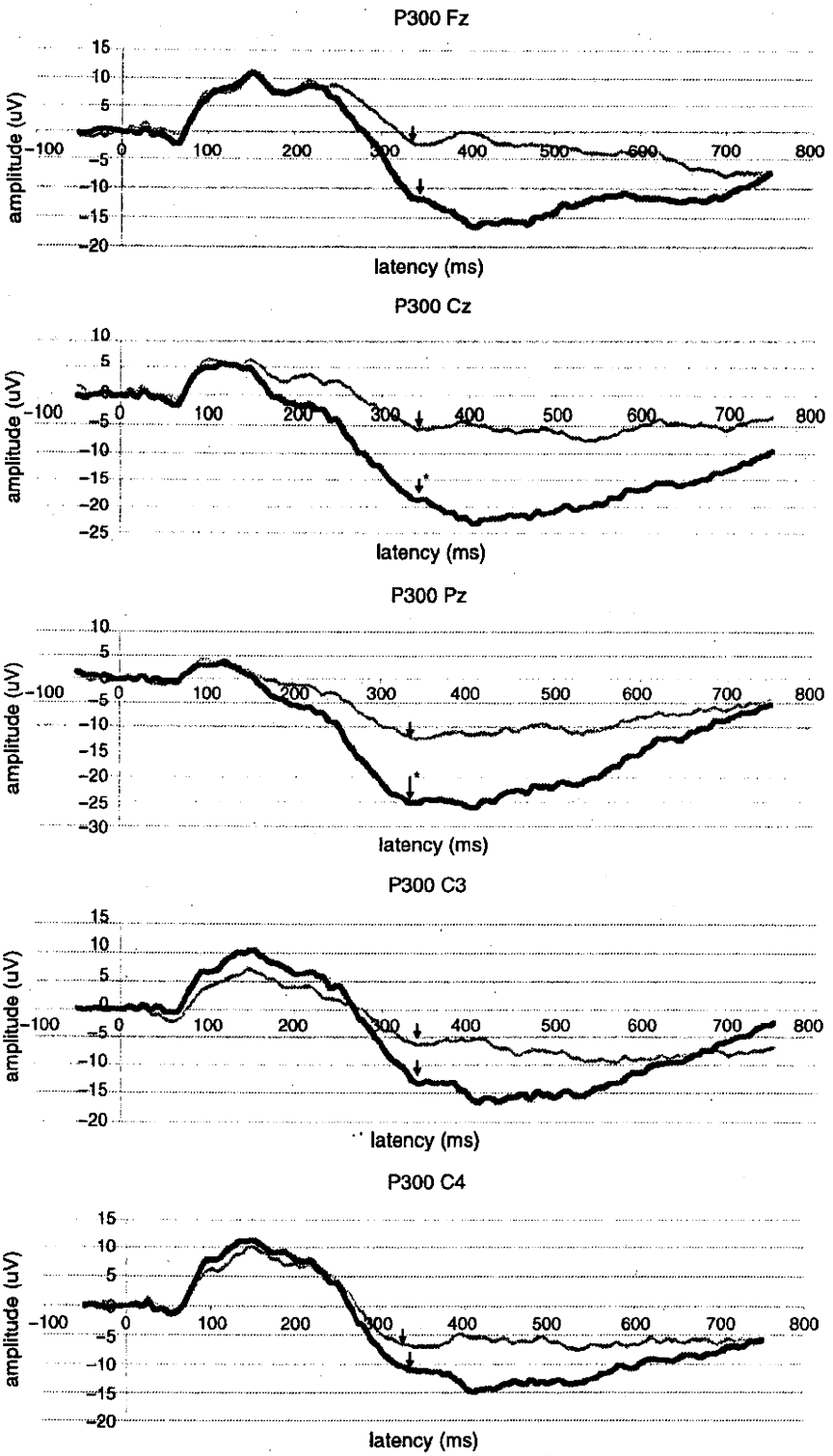

Figure 2. Grand average P300 from attention-deficit/hyperactivity disorder children (▬) before and (▬) after Concerta treatment conditions. P300 is shown by arrows. $^{*}P < 0.05$.

ADHD children was ameliorated by osmotic-release MPH treatment. However, P300 is likely to be affected by the cognitive factors present prior to P300 generation, thus limiting the significance of investigations employing solely P300 recordings. As such, we also evaluated MMN in ADHD children in the present study, the pre-P300 potentials that reflect information processing itself.[3,5]

In the present study, we reported that MMN amplitudes were increased after osmotic-release MPH treatment in ADHD children, suggesting that the automatic cerebral discrimination process might be ameliorated by osmotic-release MPH treatment, which in turn may have reduced the impulsiveness and hyperactivity in ADHD children.

With respect to the laterality of cerebral dysfunction in ADHD, it was proposed that ADHD children exhibit dysfunction in a right-sided frontal-striatal system.[13] This comprehensive morphometric analysis was consistent with the hypothesized dysfunction of right-sided prefrontal-striatal systems in ADHD children.[14] Furthermore, in an event-related functional magnetic resonance imaging (fMRI) study, ADHD children exhibited less right-sided activation in the anterior cingulate gyrus during alerting (one of the attentional networks) relative to controls.[15]

In the present study, there was no difference between the left (C3) and right (C4) P300 amplitudes or MMN amplitudes either before or after treatment, and there was no difference between the left (C3) and right (C4) P300 and MMN latencies either before or after treatment. However, the MMN amplitude after osmotic-release MPH treatment was significantly greater than that in the drug-naive situation at C4. Thus, we suggest that the right hemisphere may be competent following MPH treatment with respect to MMN.

There were two limitations to our study. First, the sample size was small. However, we examined 10 ADHD children who had no history of developmental disorder treatment, and our data showed significant changes. Second, we had no placebo-control subjects. Future studies with large samples and placebo-control subjects as measured by ERP are required to determine whether cognitive function in ADHD children was ameliorated by osmotic-release MPH treatment. In conclusion, the results of the present study suggest that both MMN and P300 are sensitive tools for measuring the pharmacological effects of osmotic-release MPH in ADHD children.

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併存障害を伴うADHDへのストラテラの使用経験

太田豊作
飯田順三

はじめに

注意欠如・多動性障害（attention-deficit/hyperactivity disorder：ADHD）は、不注意、多動性、衝動性を主症状とする発達障害であり、米国では学童において三～七％の有病率が報告されている。また、ADHDはさまざまな精神疾患が併存することが知られており、ADHDと診断された小児が併存障害を有する割合は、米国では約三分の二、日本では約八〇％とされている。主な併存障害の併存割合は、米国では反抗挑戦性障害が五〇％、行為（素行）障害が一五～二〇％、不安障害が二〇～二五％、気分障害が一五～二〇％、学習障害が一〇～二五％とされ、次いでチック障害、排泄障害、睡眠障害、吃音などが挙げられる。日本では反抗挑戦性障害が五四％、行為（素行）障害が一〇％、学習障害が二六％、排泄障害が二〇％、運動能力障害が一〇％、チック障害が九％、強迫性障害が八％、睡眠障害が六％、分離不安障害が六％、過剰不安障害が四％、気分障害が二％と報告されている。[1] 日米ともに反抗挑戦性

障害と行為（素行）障害の併存は多く、併存割合にもそれほど差がないが、気分障害の併存は米国では多く、日本では少ないという特徴が認められる。

これまでの報告では、ストラテラがＡＤＨＤにおける不注意、多動性、衝動性という中核症状を改善するだけでなく、ＡＤＨＤ患者の生活の質を高め、睡眠潜時を改善し、終日にわたる効果を示すことが示されている。それに加えて、ＡＤＨＤの併存障害を悪化させることなく、中核症状を改善することも報告されている。

本稿では、併存障害の中でも比較的併存頻度の高い反抗挑戦性障害、不安障害、気分障害、チック障害に焦点をあて、これらが併存するＡＤＨＤへのストラテラによる薬物療法に関する文献展望と使用経験を示す。

反抗挑戦性障害

反抗挑戦性障害は、権威のある人物に対する拒絶的、反抗的、挑戦的な行動が繰り返されるパターンを精神障害として定義したものである。ＡＤＨＤに併存する反抗挑戦性障害は、ＡＤＨＤの二次障害として、また、児童の適応、家族の負担を考える上でも重要な併存障害である。薬物療法では、メチルフェニデートが考慮される。この他に、衝動性が目立つ場合にはバルプロ酸やカルバマゼピンなどの抗てんかん薬が選択され、抗精神病薬や炭酸リチウムが使用されることもある。これまでの報告で、ストラテラによる薬物療法に関するものは五つある。

バングスら（Bangs, et al.）は、ＤＳＭ―ⅣでＡＤＨＤと反抗挑戦性障害の併存と診断された六～十二歳の児童二二六人を三～二十八日間のウォッシュアウトの後、二重盲検下でストラテラまたはプラセボに二対一の比で割り付け、Swanson, Nolan and Pelham Rating Scale（ＳＮＡＰ―Ⅳ）を用いて八週間の評価を行った。ＳＮＡＰ―Ⅳの二六項目は、不注意の九項目、多動性―衝動性の九項目、反抗性の八項目からなるが、観察期間を通して、不注意、多動性―衝動性、反抗性の有意な改善を認めた。(2)

カプランら（Kaplan, et al.）は九八人の児童を対象に二重盲検比較試験を行い、ストラテラ群とプラセボ群を比較

している。ストラテラ群ではプラセボ群に比べADHD―RSの総スコアやコナーズ評価尺度のADHD指標、認知スコア、多動スコアなどは有意に改善したが、反抗性スコアに有意な変化は認めなかった。[3] 同様に、ビーダーマンら(Biederman, et al.)は、DSM―ⅣでADHDと診断された六～十六歳の児童・青年五一二人を対象とした二重盲検比較試験を行った。一五八人は反抗挑戦性障害を併存していたが、その併存の有無にかかわらずADHD―RSの多動性―衝動性スコア、コナーズ評価尺度のADHD指標、認知スコア、多動スコアなどは改善したが、反抗性スコアについては反抗挑戦性障害の併存例では有意な改善を認めなかった。[4]

ニューコーンら(Newcorn, et al.)は、反抗挑戦性障害を併存する八～十八歳のADHDの児童・青年に対するストラテラの用量依存性の効果を検討している。その結果、反抗挑戦性障害の併存例においてもADHDの中核症状、生活の質を同様に改善するが、反抗挑戦性障害の併存しないADHD群では一・二mg/kg/日から有意な改善がみられるのに対し、反抗挑戦性障害の併存するADHD群では一・八mg/kg/日まで使用しないと有意な改善は認められなかった。[5]

一方、ストラテラによるADHD患者の再発予防効果に反抗挑戦性障害の併存の有無が与える影響を調べた研究[6]がある。十週間の非盲検試験でADHD症状が寛解した四一六人の六～十五歳の児童・青年を、ストラテラ継続群とプラセボ投与群に分け、九ヵ月間にわたる追跡を行ったところ、再発に至る日数に有意な違いはみられなかった。

これらの結果から、反抗挑戦性障害の併存例においても、ストラテラは反抗性を悪化させることなく、不注意、多動性、衝動性といった中核症状を改善するといえる。また、その際のストラテラの用量としては、ADHD単独例に比べ反抗挑戦性障害の併存例では高用量が必要となる可能性も示している。

反抗挑戦性障害を併存する症例

症例一　小学三年（九歳）の男児

満期産で出生し、始歩および始語は一歳で、二語文は二歳であった。乳幼児健康診査では何も指摘されなかった。歩き始めるとよく迷子になった。二歳から通所した保育所では、友達をすぐに叩き、玩具を投げるなどしてよく物を壊し、これは家でも同様であった。保育所の先生からは「しつけがなっていない」と指摘されたため、本児の問題行動に対して、両親は厳しく叱っていた。小学校に入学後、授業中の離席が目立ち、担任の質問が終わる前に発言するなどした。家では、言いつけを守らないため叱られることが多かった。学年が上がるにつれて、次第に大人に対して反抗的になった。特に三年生になり担任が代わると「うるさいハゲジジイ」など言葉づかいが荒くなった。また、授業に集中しないことが増えていき、同時に担任から注意されることが多くなったため、担任との衝突は繰り返された。また、家でも宿題をせず、両親から注意され叱られてはかんしゃくを起こしたり、「黙っとけ、ボケ」などと言ったりした。級友とも些細なことで喧嘩になり、本児は叩く蹴るの暴力を振るうため、心配した母親とともに「反抗的で暴力を振るう」という主訴で当科初診となった。ADHDと反抗挑戦性障害の併存と診断した。

本児は身長一三四センチメートルで体重が三〇キログラムであったため、ストラテラ服薬開始後、段階的に増量し一日用量を五〇ミリグラムとした。その後、徐々に多動性や衝動性の改善が認められた。また、ストラテラの一日用量を五〇ミリグラムとしてから約六週間後には、注意されて「うるさい」と怒鳴ることはあるが頻度は少なくなり、級友と喧嘩する回数も減少し、日常生活で笑顔がみられることも多くなったという。現在も筆者のもとに通院を継続している。

本症例では、ストラテラによる薬物療法の開始後にADHD症状とともに反抗性も改善傾向を示した。薬物療法以外に、診察時に家族に対して「つい叱りたくなる行動に目がいってしまうが、必ず良いところもある。叱るだけでな

く褒めたり認めたりすることも重要である」などADHDに関する心理教育を行っていたため、家族もそれを意識して実行していた。そのことで本児の自尊感情が良好なものとなり、本症例の全体的な症状改善に寄与したのかもしれない。しかし、このような自尊感情の変化が生じるまでには時間を要するため、比較的効果の出現が早い薬物療法は必要であり、本症例ではストラテラがADHD症状と反抗性の改善に多大に寄与したと考えている。

不安障害

不安障害は主に、パニック障害、恐怖症、社会恐怖、強迫性障害、ストレス障害、全般性不安障害に分けられる。併存障害に明確な治療ストラテジーが存在する場合は、それをADHD治療に併せて行っていくことが基本となる。しかし、児童思春期においてストレス障害と強迫性障害にはある程度の治療ストラテジーが存在するが、その他の不安障害に関しては未だ明確なストラテジーが確立されているとは言いがたい。

不安障害が併存するADHDに対するストラテラの有効性の検討は、ゲラーら（Geller, et al.）が報告している[7]。ゲラーらは、全般性不安障害、分離不安障害、社会恐怖の少なくとも一つを併存する八～十七歳のADHDの児童・青年一七六人を対象として、二重盲検下でストラテラ群とプラセボ群に無作為に割り付け、十週間フォローアップした。ストラテラ群とプラセボ群を比較したところ、ADHD―RSの総スコアの変化量と小児不安評価尺度の総スコアの変化量ともにストラテラ群で有意に改善していた。このことは、ストラテラがADHD症状と不安症状の両方に奏功している可能性を示唆する。

気分障害

気分障害には、うつ病性障害、双極性障害、特定不能の気分障害がある。ADHDに併存する気分障害の治療方法は、気分障害本来の治療方法と基本的には同様で、特に双極性障害や大うつ病性障害の治療は薬物療法が中心となる。したがって、双極性障害の併存する患者には気分安定

薬や抗精神病薬、大うつ病性障害の併存する患者には選択的セロトニン再取り込み阻害薬を考慮することとなる。

ＡＤＨＤに大うつ病を併存している十二～十八歳の青年一四二人を対象に九週間の二重盲検比較試験を行ったところ、ストラテラ群はプラセボ群に比べて、ＡＤＨＤ－ＲＳの総スコアが有意に低下した[8]。また、ストラテラ群はうつ状態の重症度を表す評価尺度も減少したが、それはプラセボ群に比べ有意ではなかった。

また、七例のケースレポートとしての報告であるが、双極性障害を併存したＡＤＨＤにストラテラを使用し、全例で躁状態の出現もなく良好な忍容性が認められ、七例中五例でＡＤＨＤ症状の改善が認められたという報告[9]もある。

チック障害

チックは幼児期の後半から児童期に生じやすく、それは不随意的、突発的、急速、反復性、非律動的、常同的な運動または発声のことで、運動性チックと音声チックがある。運動性チックは、瞬きや首をすくめたり、肩を動かしたり、または跳び上がるといったものである。音声チックは、咳払いや鼻を鳴らしたり、汚言（コプロラリア）などである。複数の運動性チックと一つ以上の音声チックが一年以上続くとトゥレット症候群と診断される。

チック症状に対する薬物療法は、ハロペリドール、ピモジド、リスペリドンといった抗精神病薬の使用が中心となる。ＡＤＨＤの治療薬の一つであるメチルフェニデートはチック症状を悪化させる可能性があることからＡＤＨＤとチック障害の併存例では使用が困難であり、メチルフェニデートの徐放剤であるコンサータの添付文書には運動性チックおよびトゥレット症候群には使用禁忌と記されている。しかし、ＡＤＨＤとチック障害の併存例でも、チック症状が重度でない場合はＡＤＨＤ症状の改善を目的にメチルフェニデートの使用も検討される。また、ＡＤＨＤとチック障害の併存例に対してはクロニジンの有効性も報告されている。クロニジンは、効果の出現までに六～八週間と時間が比較的かかるものの、チック症状だけでなくＡＤＨＤ症状に対しても改善効果が期待される。

ＡＤＨＤにトゥレット症候群または慢性運動性チック障害が併存している七～十七歳の患者一四八人を対象に十八週間の二重盲検比較試験を行ったところ、ストラテラ群においてＡＤＨＤ－ＲＳの総スコアの有意な改善を認めただけでなく、Yaleチック評価尺度（ＹＧＴＳＳ）の総スコアなどにおいてストラテラ群の方がプラセボ群よりも有意に改善していた[10]。このことは、ストラテラがチック症状を悪化させず、むしろ改善するとともにＡＤＨＤの中核症状も改善することを示している。

トゥレット症候群を併存する症例

症例二　小学二年（八歳）の男児

満期産で出生し、一歳で始語、一歳三ヵ月に始歩がみられた。二語文は二歳二ヵ月で乳幼児健康診査では何も指摘されなかった。両親と三歳年上の兄との四人暮らしであった。幼稚園ではいつも元気な子と言われた。小学校に入学すると持ち物を玄関に置いていても忘れるような不注意が目立ちだし、授業のノートは黒板の写し忘れや誤字が多く、机の中は持ち帰るのを忘れたプリントでいっぱいだった。また、授業中にキョロキョロし、椅子に座っているときに常に足をバタバタ動かしているなどの多動性が認められた。これらのために、担任や両親から叱られることが多かった。

小学一年の七月から一時的に瞬きを繰り返すことが多くなり、その後肩をすくめる突発的な運動がみられるようになった。冬休みの直前に母親は担任に相談したところ、「家でも学校でも叱り過ぎかもしれませんね。双方で意識して叱り過ぎないようにしましょう」ということになった。小学一年の二月には肩をすくめる運動はみられなくなったが、不注意なところや多動性は変わらず認められた。小学二年になっても不注意なところや多動性は変わらず認められ、担任が代わったこともあり学校で叱られる回数は増えた。小学二年の五月頃から、鼻をすするように鳴らすことが頻回になり、七月からは「アホ、アホ」と汚言（コプロラリア）もみられるようになったため、担任の勧めもあり両親とともに「突然「アホ、アホ」と言い出し、落ち

着きがなく、忘れ物が絶えない」という主訴で八月に当科初診となった。ＡＤＨＤとトゥレット症候群の併存と診断した。

両親にＡＤＨＤとトゥレット症候群に関する心理教育を行うとともに、「アホ、アホ」というようにコプロラリアも認められたためチック症状に対するリスペリドンを用いての薬物療法を始めた。リスペリドンを就寝前に一ミリグラム服用とした。その後、鼻を鳴らす音声チックの頻度が増加し、コプロラリアも変化がないため同薬を一・五ミリグラムに増量したが、チック症状の改善も認められず、ＡＤＨＤの症状である不注意や多動性も改善を認めなかった。また、徐々に眠気が増強しはじめ、嘔気も出現したため九月下旬にリスペリドンによる薬物療法を中止した。

その後休薬期間を設け、十月からはストラテラによる薬物療法を開始した。本児が身長一二六センチメートルで体重が二五キログラムであったため、ストラテラ一〇ミリグラムを一日二回に分けての服用とした。その後同薬を一日用量二〇ミリグラムとして二ヵ月後での評価では、鼻を鳴らす音声チックはみられるが「アホ、アホ」というコプロラリアは消失し、運動性チックとしての瞬きは時折認められるという状態であった。ＡＤＨＤ症状に関しては、忘れ物が減り、家の食卓では座っていても絶えず足を動かしているが学校では目立たず、叱られる回数は減り授業に支障はなくなっているという状態であった。

本症例での大きな問題点は、チック症状であるコプロラリアが認められており、それが級友など周囲との関係性を悪化させてしまいやすいことと、不注意や多動性が原因で本児が叱られやすくなっていることの二点であった。臨床的には、リスペリドンによって多動性が改善することも経験するため、チック症状の改善を主に期待してリスペリドンによる薬物療法から開始したが、効果がみられず副作用の出現もあったため中止とした。次に、主にＡＤＨＤ症状の改善を期待してストラテラによる薬物療法とした。ＡＤＨＤ症状もチック症状も残存しているものの、両症状ともに改善傾向であり特に問題点として挙げた二点が解消された。

まとめ

ＡＤＨＤは多彩な併存障害を伴う発達障害であり、その存在を考慮した上で薬物療法の薬剤選択を行う必要がある。ストラテラは非中枢神経刺激薬であり、これまでのランダム化比較試験の成績から、反抗挑戦性障害、不安障害、気分障害およびチック障害が併存するＡＤＨＤに対しても、これらの併存障害を悪化させることなく、ＡＤＨＤの中核症状を改善することが示されている。また不安障害やチック障害では、ストラテラにより併存障害の症状が改善することも期待できる。使用経験として、二症例を提示したが両者ともＡＤＨＤの中核症状だけでなく併存障害の症状も改善した。

今後は日本における使用経験をさらに収集する必要があるが、ストラテラの登場により日本におけるＡＤＨＤ治療の幅が大きく広がったといえるであろう。

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Impairment of unconscious, but not conscious, gaze-triggered attention orienting in Asperger's disorder

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ABSTRACT

Impairment of joint attention represents the core clinical features of pervasive developmental disorders (PDDs), including autism and Asperger's disorder. However, experimental studies reported intact gaze-triggered attentional orienting in PDD. Since all previous studies employed supraliminal presentation of gaze stimuli, we hypothesized that individuals with PDD may be impaired not in conscious but in unconscious gaze-triggered attention shift. We tested the hypothesis in a group of Asperger's disorder ($N = 12$) and age- and gender-matched controls ($N = 13$), using a cueing paradigm with supraliminal and subliminal presentation of gaze cues. Under supraliminal conditions, the gaze cueing effect was evident in both groups. Under subliminal conditions, the Asperger group, unlike the control group, did not show the gaze cueing effect. These results indicate the impairment of unconscious, but not conscious, joint attention in Asperger's disorder, which may underlie some clinical findings of social malfunction in PDD.

1. Introduction

Individuals with pervasive developmental disorders (PDDs), including autism and Asperger's disorder, are characterized primarily by qualitative impairments of social interaction (American Psychiatric Association, 2000; Matson, Compton, & Sevin, 1991). One of the most evident features of their social impairment is the deficit in joint attention (Mundy, Sigman, & Kasari, 1994). For example, when the attending physician suddenly averts his gaze to look at environmental objects during a clinical interview, an individual with PDD fails to follow his gaze direction (Okada, Sato, Murai, Kubota, & Toichi, 2003).

In contrast to such obvious clinical evidence of impaired joint attention, several experimental studies have found a normal ability to shift attention with another's gaze reflexively in PDD (Chawarska, Klin, & Volkmar, 2003; Johnson et al., 2005; Kylliainen & Hietanen, 2004; Okada et al., 2003; Senju, Tojo, Dairoku, & Hasegawa, 2004; Swettenham, Condie, Campbell, Milne, & Coleman, 2003; Vlamings, Stauder, van Son, & Mottron, 2005; for a review see Nation & Penny, 2008). The studies have used Posner's (1980) cueing paradigm to examine joint attention (c.f., Frischen, Bayliss, & Tipper, 2007). For example, Okada et al. (2003) presented a face with eyes directed left or right to individuals with PDD, and to controls with no developmental disorder. Then, a target appeared to the right or left side of the face. The reaction time (RT) to detect the target

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was shorter at a validly cued location than at an invalidly cued location in both PDD and control participants. These results suggest that computerized experiments using a conventional gaze cueing paradigm cannot reveal the impaired joint attention in PDD.

Experimental social psychological studies have revealed that our social interactions are full of adaptive unconscious processes (Wilson, 2002). A recent study revealed that gaze-triggered attention could even occur unconsciously (Sato, Okada, & Toichi, 2007). Based on these data, we hypothesized it would be unconscious, rather than conscious, gaze-triggered attention shift that is impaired in PDD. Here we tested this hypothesis in a group of Asperger's disorder and age- and gender-matched typically developing controls. We used the same cueing paradigm with supraliminally or subliminally presented gaze cues, as in a previous study (Sato et al., 2007).

2. Methods

2.1. Participants

The Asperger group (3 females, 9 males; mean ± *SD* age = 17.2 ± 6.3 years) consisted of 11 (2 females, 9 males) with Asperger's disorder and 1(female) with PDD not otherwise specified (PDD-NOS), who did not satisfy all the diagnostic criteria for Asperger's disorder but exhibited mild symptoms of PDD. The diagnoses, based on the DSM-IV-TR (American Psychiatric Association, 2000), were made by psychiatrists with expertise in developmental disorders. Neurological and psychiatric problems other than those associated with PDD were ruled out. Participants were taking no medication. The Full-scale IQ, measured by the WAIS-R or WISC-R, of all participants in the Asperger group scored in the normal range (Full-scale IQ = 106.8 ± 9.3; Verbal IQ = 106.4 ± 13.1; Performance IQ = 104.2 ± 10.0). Participants in the control group (3 females, 10 males; mean ± *SD* age = 19.7 ± 1.9 years) were matched for age and gender with the Asperger group. All participants had normal or corrected-to-normal visual acuity. After the procedure and purpose of the study were explained fully and before testing, written informed consent was obtained from the participants or their parents.

2.2. Experimental design

The experiment was constructed as a two-factorial mixed randomized-repeated design, with group (Asperger or control) as the randomized factor, and presentation condition (subliminal or supraliminal) as the repeated factor.

2.3. Apparatus

The events were controlled by SuperLab Pro 2.0 (Cedrus) and implemented on a Windows computer (MA55J, NEC). The stimuli were presented on a 19-in. CRT monitor (GDM-F400, Sony) with a refresh rate of 100 Hz and a resolution of 1024 × 768 pixels. The participants' responses were recorded using a response box (RB-400, Cedrus).

2.4. Stimuli

The gaze cues consisted of schematic faces in which the eye gaze was directed toward either the left or right. Masks were mosaic patterns that covered all of the facial features of the cue stimuli. The cues and masks subtended 6.5° vertically × 6.5° horizontally. The target was an open circle subtending 1.0° vertically × 1.0° horizontally. These stimuli consisted of a black line drawing on a white background.

2.5. Procedure

The procedure was identical to that of a previous study (Sato et al., 2007). The experiments were conducted individually in a small room. The participant was seated comfortably with her/his head supported by a chin-and-forehead rest located 0.57 m from the screen.

A threshold assessment session was first conducted. The stimulus onset asynchrony (SOA) between the target and mask was manipulated. To assess the upper limit of SOA for subliminal presentation in each participant, blocks of 20 subliminal cue presentation trials, i.e., 10 each for the left and right gaze directions, were prepared. In each trial, after the presentation of a fixation point, i.e., a small black "+" lasting 680 ms, the gaze cue was presented in the center of the monitor, after which the mask was presented in the same location. The presentation time of the mask was adjusted so that the total presentation period of the gaze cue and the mask was 200 ms. The order of gaze direction was randomized. The participant was asked to orally answer the question, "Did you see the gaze? If so, report the direction of the gaze." They were also asked not to guess at answers. The participants responded either "Yes" or "No," and in the case of the former, they then reported the gaze direction that they had seen. Starting with 10 ms, the SOA was prolonged by 10 ms increments. After the participants finished each block, the performance was investigated. If the participant correctly recognized at least 1 of the 20 stimuli, the corresponding SOA was regarded as the lower limit of conscious awareness for the cue for that participant, and an SOA 10 ms shorter than that limit was used in the trial session. The mean (±*SD*) SOA was as 19.2 ± 10.9 and 14.7 ± 7.8 ms for the Asperger and control groups, respectively (two-tailed *t*-test, $t(23) = 1.21$, *n.s.*).

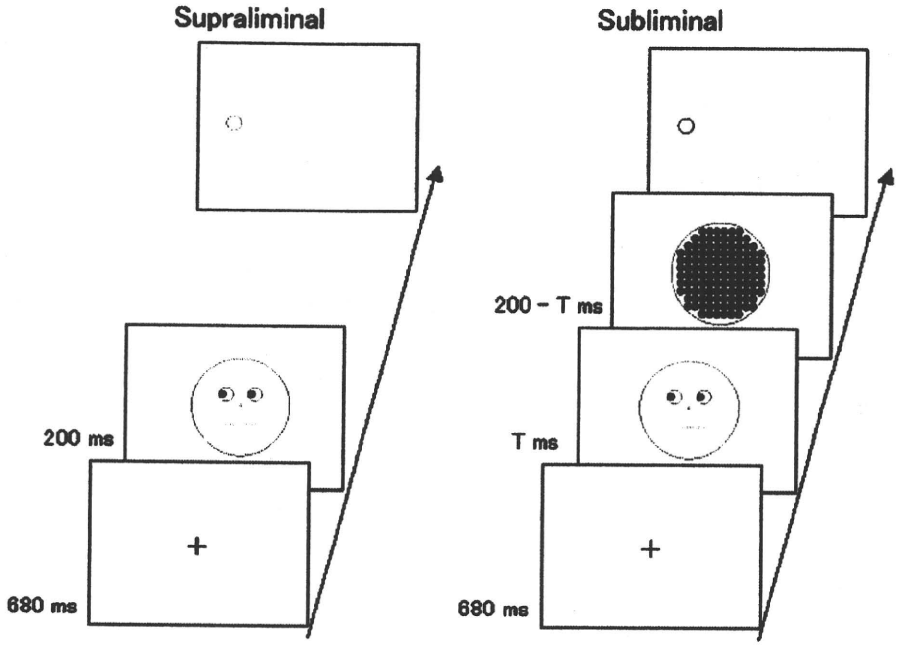

Fig. 1. Illustrations of stimulus presentations. In the subliminal presentation, the presentation time of the gaze cue (T) was adjusted for each participant's threshold and the presentation period of the mask was also adjusted so that the total period of the gaze cue and the mask was 200 ms.

The trial session was then conducted. The participant completed a total of 144 trials, presented in two blocks of 72. Each block contained an equal number of valid and invalid trials for each presentation condition. The order of cue validity was randomized within each block. The order of presentation condition was counterbalanced across participants. At the beginning of each block, the participant received 10 practice trials. A short break was interposed after 36 trials in each block, and a longer break was interposed after each block.

For each trial (Fig. 1), a fixation point, i.e., a small black "+," was presented for 680 ms at the center of the screen. The gaze cue was then presented at the same location. Subsequently, a target was presented in either the left or right visual field (5.0° apart from the center) until a response was made. The participant was instructed to specify as quickly as possible whether the target appeared on the left or right side of the screen by pressing the corresponding key on the switch box using the left or right index finger, respectively.

After the completion of all trials, debriefing was conducted and the participant was asked whether she/he had consciously perceived the gaze cues in the subliminal presentations. We confirmed that none of the participants had consciously perceived the gaze cues in the subliminal presentations.

2.6. Data analysis

The median correct reaction time (RT) under each condition was calculated for each participant. The differences in RT between valid and invalid conditions were then calculated as a measure of the gaze cueing effect as in previous studies (e.g., Okada, Sato, & Toichi, 2006). The RT differences were analyzed using a 2 (group: Asperger or control) × 2 (presentation condition: subliminal or supraliminal) analysis of variance (ANOVA). For significant interactions, follow-up multiple comparisons were conducted for the group factor using *t*-tests (two-tailed) with the Bonferroni correction. One-sample *t*-tests (two-tailed) were also performed to test for differences from zero with the Bonferroni correction.

Preliminary analyses were conducted for error percentages. The error rates were small (<5%) and there was no evidence of a speed-accuracy trade-off phenomenon. Hence, we report only the RT results.

3. Results

The ANOVA for the differences in RT between validly and invalidly cued conditions (Fig. 2) revealed a significant interaction of group × presentation condition ($F(1,23) = 5.90$, $p < .05$). The main effect of presentation condition was also significant ($F(1,23) = 38.88$, $p < .001$).

Follow-up analyses for the interaction revealed that there was a significant between-group difference in the subliminal condition ($t(23) = 3.33$, $p < .001$), which indicated a larger RT difference for the control group than for the Asperger group. There was no significant between-group difference in the supraliminal condition ($t(23) = 1.34$, *n.s.*).

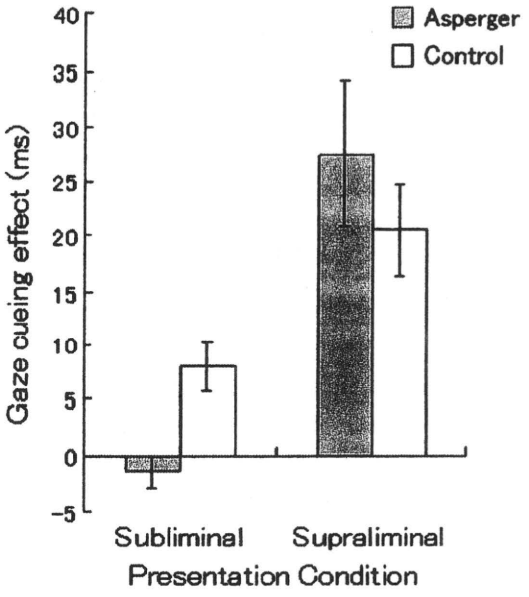

Fig. 2. Mean (with SE) gaze cueing effect (i.e., differences in reaction time between validly and invalidly cued conditions).

Bonferroni-corrected one-sample *t*-tests were performed to test for differences from zero. All conditions differed significantly from zero ($ts > 2.87$, $ps < .05$), with the exception of subliminal presentations to the Asperger group ($t(11) = 0.92$, *n.s.*).

4. Discussion

Congruent with previous studies that used the supraliminal presentation of gaze cues (Nation & Penny, 2008), we found a gaze cueing effect for both the Asperger and control groups under supraliminal conditions. These data confirm that conscious gaze-triggered attention orienting is not impaired in individuals diagnosed with PDD.

Under subliminal conditions, however, there was a gaze cueing effect in the control group, but not in the Asperger group. The triggering of attention orientation in participants without developmental disorders by the unconscious gaze cue is consistent with previous results (Sato et al., 2007). The impairment in the orienting response triggered by an unconscious gaze cue in Asperger's disorder is a novel finding. This finding seems consistent with previous behavioral studies that have reported impairment in the unconscious processing of facial stimuli in individuals with PDD (e.g., Hall, West, & Szatmari, 2007). The results support the hypothesis that individuals with PDD have impaired unconscious, but not conscious, gaze-triggered attention.

Our results can explain the discrepancy between previous clinical (Mundy et al., 1994) and experimental (Nation & Penny, 2008) findings on joint attention in PDD. Psychophysical studies have shown that, contrary to what intuition might suggest, humans consciously perceive only very restricted areas within the range of areas available for immediate attention (Simons & Rensink, 2005). Consistent with this notion, psychological studies have indicated that social behaviors are heavily influenced by unconscious processing (Wilson, 2002). In particular, previous research has found that gaze-triggered attention orienting occurs unconsciously (Sato et al., 2007). Thus, individuals that exhibit typical developmental milestones have at least two mechanisms to achieve automatic joint attention: conscious processing of the gazes of others that occur within restricted attended areas and unconscious processing of the gazes of others that occur within broader unattended areas. Our results indicate that individuals with PDD have access to only a single conscious mechanism for the achievement of joint attention; therefore, these individuals may fail to show joint attention in relation to individuals outside of the range of conscious attention.

Our finding of impaired unconscious gaze processing in individuals diagnosed with PDD corroborates evidence from neuroscientific literature. A neuroimaging study of typically developing participants reported the involvement of the amygdala in the unconscious processing of gaze (Whalen et al., 2004). A study of patients with unilateral amygdala incisions indicated that the amygdala is involved in gaze-triggered attention orienting (Okada et al., 2008). Considering the neural network from which the amygdala receives visual input, i.e., the subcortical pathway via the pulvinar and superior colliculus (Adolphs, 2002), it is possible that the amygdala processes the information derived from gaze, even before conscious awareness has emerged. Postmortem histopathological (e.g., Schumann & Amaral, 2006) and neuroanatomical imaging (e.g., Schumann et al., 2004) studies have reported a pronounced abnormality of the amygdala in individuals diagnosed with PDD. Neuroimaging studies have reported that these individuals show reduced activity of the amygdala in the processing of gaze (e.g., Baron-Cohen et al., 1999). These data suggest that dysfunction of the amygdala may be the neural background of the impairment of the unconscious gaze-triggered attention orienting in individuals with PDD.

In contrast, the conscious awareness of visual stimuli is implemented in the cortical visual areas (Treisman & Kanwisher, 1998). Neuroimaging studies in normatively developing participants showed the activation of some cortical visual areas, including the superior temporal sulcus (STS) region, in response to supraliminally presented gaze (e.g., Hoffman & Haxby, 2000). A neuroimaging study in individuals with PDD also reported the activation of the STS region in the conscious processing of gaze (Baron-Cohen et al., 1999). These data suggest that the cortical pathways involved in the conscious processing of gaze are not impaired in PDD.

Controversy persists about whether automatic processing can be identified with the absence of consciousness (Tzelgov, 1997). Our results indicate that automatic gaze-triggered attention consists of conscious and unconscious processes, with one dissociable from the other. It has been proposed that automatic processes could derive from either heredity or practice (Hasher & Zacks, 1979). We speculate that individuals with PDD may have innate impairments in the unconscious subcortical system, but can acquire, through practice, the conscious cortical system that allows joint attention.

In summary, our results showed gaze-triggered attentional orienting for both the Asperger and control groups under supraliminal conditions; however, the Asperger group, unlike the control group, did not show the gaze cueing effect under subliminal conditions. These results indicate the impairment of unconscious, but not conscious, joint attention in Asperger's disorder, which may underlie some clinical findings of social malfunction in PDD.

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ADHDの神経生物学

―最新の知見―

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抄録：注意欠如／多動性障害（ADHD）の罹患性には，ドパミンをはじめとするモノアミンの受容体やトランスポーターの遺伝子多型が関与しており，ドパミン活性を調べた研究からも皮質下領域を中心にドパミン神経系の機能低下があることが示唆されている。また，ドパミン神経の投射を受ける前頭皮質や前部帯状回皮質などの脳部位の形態的，機能的異常や大脳皮質の成熟遅延が報告されている。ADHDの神経心理学的な検討とこれらの脳部位の機能を考え合わせ，ADHDの機能障害を実行機能と報酬系の機能不全から説明する二重経路モデル（dual pathway model）が提唱されている。しかし，ADHDの個々の臨床症状や治療反応性との関係はどうか，これらの脳部位の機能や神経心理学的機能が年齢とともにどのように変化するのかについては，まだ十分に明らかにされておらず，今後の検討が求められる。　精神科治療学　25(6)；735-740，2010

Key words：*attention deficit/hyperactivity disorder, neurobiology, executive function, reward system*

I．はじめに

注意欠如／多動性障害（ADHD）は，7歳以前より認められる発達水準に不相応な不注意，多動性-衝動性という行動上の特徴によって診断される障害である[1]。DSMにおけるADHD概念は，DSM-IIの児童期における多動反応，DSM-IIIにおける注意欠如障害，DSM-III-Rにおける注意欠如多動性障害，DSM-IVにおける注意欠如／多動性障害へと変遷を遂げた。今日では，多動性-衝動性と不注意のいずれかがあればADHDと診断され，混合型，多動性-衝動性優勢型，不注意優勢型に分類されている。しかし，一方，ICD-10ではADHDは多動性障害と表現され「F8心理的発達の障害」ではなく「F9小児期および青年期に通常発症する行動および情緒の障害」に分類されている。すなわち，広汎性発達障害などとは異なり，情緒障害と同じカテゴリーに含められている。しかし，近年のADHDに関する生物学的知見によれば，この障害が，遺伝的要因と環境要因によって規定され，周産期異常がそのリスクを高めること，脳内の各部位に解剖学的／機能的変化，神経伝達物質レベルでの神経化学的異常があることが明らかになり，生物学的基盤をもった発達障害であることがコンセンサスとなりつつある。本稿では，ADHDの神経生物学的基盤に関する生物学的エビデンスをまとめ，そこから導

Neurobiology of ADHD：an update.

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